

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY


(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D 08 APR 2005

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Applicant's or agent's file reference 101046-1 WO		<b>FOR FURTHER ACTION</b>		See Form PCT/PEA/416
International application No. PCT/GB2004/001939		International filing date (day/month/year) 04.05.2004	Priority date (day/month/year) 07.05.2003	
International Patent Classification (IPC) or national classification and IPC A61K31/498, A61K31/517, A61K45/06, A61P35/00, A61P9/12				
Applicant ASTRAZENECA AB et al.				
<p>1. This report is the International preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> sent to the applicant and to the International Bureau) a total of sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>				
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input checked="" type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>				
Date of submission of the demand  29.11.2004		Date of completion of this report  31.03.2005		
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized Officer Telephone No. +49 89 2399-		



**INTERNATIONAL PRELIMINARY REPORT  
ON PATENTABILITY**

International application No.  
PCT/GB2004/001939

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**Box No. I Basis of the report**

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1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
  - ☐ publication of the international application (under Rule 12.4)
  - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements\*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

**Description, Pages**

1-96 as originally filed

**Claims, Numbers**

1-12 as originally filed

**Drawings, Sheets**

1/3-3/3 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
  - ☐ the claims, Nos.
  - ☐ the drawings, sheets/figs
  - ☐ the sequence listing (*specify*):
  - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
  - ☐ the claims, Nos.
  - ☐ the drawings, sheets/figs
  - ☐ the sequence listing (*specify*):
  - ☐ any table(s) related to sequence listing (*specify*):

\* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT  
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**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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1. Statement

Novelty (N)	Yes: Claims	1-12
	No: Claims	
Inventive step (IS)	Yes: Claims	1
	No: Claims	2-12
Industrial applicability (IA)	Yes: Claims	1-12
	No: Claims	

2. Citations and explanations (Rule 70.7):

**see separate sheet**

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**Box No. VII Certain defects in the international application**

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The following defects in the form or contents of the international application have been noted:

**see separate sheet**

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Reference is made to the following documents:**

D1: WO 01/ 74360 (cited in the application)  
D2: WO OO/ 47212 (cited in the application)  
D3: US-A-5 770 599  
D4: WO 02/ 092579

**2. Novelty**

None of the cited prior art documents discloses a combination of an anti-angiogenic agent with an inhibitor of the Src family of non-receptor tyrosine kinases nor its therapeutic use.

Prior art documents D1 (claims 1, 4-6, 9-11; p. 1, l. 31-p. 2, l. 3) and D2 (p. 2, l. 15-21; ex. 238; claim1) both disclose the use of the same anti-angiogenic agents as the present application for the treatment of diseases associated with angiogenesis, which are as the diseases defined on p. 8, l. 4-9 of the present application. Furthermore, it is known from D1 that VEGF tyrosine kinase inhibitors lead to a sustained increase in blood pressure (p. 4, l. 3-5).

The therapeutic use of anti-angiogenic agents of the same structure as claimed in the dependent claims of the present application for the treatment of cancer is further disclosed in D3 (claims 18, 19).

Inhibitors of the Src family of non-receptor tyrosine kinases of a 4-anilinoquinazoline structure are known for the treatment of solid tumour diseases from D4 (claim10). There is, however, no disclosure in the published prior art that inhibitors of the Src family of non-receptor tyrosine kinases lower blood levels.

As a result, the subject-matter of claims 1-12 of the present application seems to be novel over the cited prior art (Art. 33(2) PCT).

**3. Inventive Step**

Although the subject-matter of independent claims 2, 5, 7 and 9 of the present application seems to be novel in view of the cited prior art it is not inventive (Art. 33(3) PCT).

The selection of an anti-angiogenic agent and a Src kinase inhibitor for use in the treatment of cancer according to independent claims 2, 5, 7 and 9 of the present application seems to be obvious in view of the cited prior art as each of the active compounds is known for its use in the treatment of cancer (see above).

The discovery of additional items of knowledge about further mechanisms of action (normotensive effect) of independent claims 2, 7 and 9 of the present application underlying the therapeutic application (anti-cancer treatment) cannot be regarded as inventive unless a new technical application is achieved.

With regard to the subject-matter of claim 5 no convincing evidence has been presented in order to show that the combination product acts synergistically.

Dependent claims 3, 4, 6, 8 and 10-12 do not contain additional technical features which might establish an inventive step over prior art; these claims are only allowable in combination with patentable independent claims (Rule 29(4) EPC).

**Re Item VII**

**Certain defects in the international application**

The expression "disease state associated with angiogenesis" of claim 1 is not clear and should be replaced by the definition given on p. 8, l. 4-9 of the description of the present application (Art. 6 PCT).